PQLI®
Guide Series

Product Quality Lifecycle Implementation (PQLI®)
from Concept to Continual Improvement

Part 1 – Product Realization using Quality by Design (QbD): Concepts and Principles

including Overview, Criticality, Design Space, and Control Strategy



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Preface

The global pharmaceutical industry and regulators are responding to the challenge of significantly improving the way drug development and manufacturing is managed. New concepts are being advanced and applied, including enhanced, quality by design approaches to product and process development and introduction into manufacturing with a focus on product and process understanding.

The international regulatory community has outlined their position on these new "Science- and Risk-Based Approach" concepts in the ICH Q8, Q9, Q10, and Q11 quality guidelines, where guidance is given on applying these concepts to drug substance and drug product across the entire drug life cycle.

Part 1 – Product Realization using Quality by Design (QbD): Concepts and Principles provides an overview as an introduction to and a summary of the Guide Series, and elaborates on the concepts of criticality, design space, and control strategy as introduced in ICH Q8, Q9, Q10, and Q11. How these concepts are applied during development and in manufacturing is discussed and exemplified.

Benefits of using enhanced, quality by design approaches are also discussed.

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Topic I

Overview of Product Realization

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1 Introduction

This is an overview of the ISPE Guide Series: Product Quality Lifecycle Implementation (PQLI) from Concept to Continual Improvement, which is an output from ISPE Product Quality Lifecycle Implementation (PQLI®) program. It is an introduction to and an overview of the Guide Series. Product realization is the achievement of a product with the quality attributes appropriate to meet the needs of patients, health care professionals, regulatory authorities (including compliance with marketing authorization), and internal customers' requirements.

This Overview and the subsequent ISPE PQLI Guide Series address product and process development, transfer to, and establishment of, commercial manufacture and continual improvement using science- and risk-based (i.e., enhanced, Quality by Design (QbD)) approaches. The Series considers how technical activities in the product lifecycle operate under a pharmaceutical quality system.

In Part 1, Product Realization using QbD: Concepts and Principles, in addition to Topic I Overview, the following topics are addressed:

- Criticality
- Design Space
- Control Strategy

In Part 2, Product Realization using QbD: Illustrative Example, there is description of an example of application of the enhanced, quality by design approach to product realization. It shows the development and introduction into manufacturing of a small molecule formulation and associated manufacturing process, and part of the drug substance synthetic route using enhanced, quality by design approaches.

The Guide Series uses ICH Guidelines Q8(R2), Pharmaceutical Development; Q9, Quality Risk Management; Q10, Pharmaceutical Quality System, and Q11, Step 2, Development and Manufacture of Drug Substances, as a basis, together with other relevant ICH Guidelines, Questions and Answers and Points to Consider (References 1, 6, 7, 8, and 15, Appendix 1).

1.1 Objective

The objective of this Guide Series is to provide "how to" guidance when implementing technical activities using the science- and risk-based approach throughout the product lifecycle.

Part 1, Product Realization using QbD: Concepts and Principles and Part 2, Product Realization using QbD: Illustrative Example provide a range of "how to" tools for practitioners developing products and their manufacturing processes using the enhanced, Quality by Design (QbD) approach described in ICH Guideline, Q8(R2) (Reference 1, Appendix 1). These give more insight than is given in the ICH Guidelines, and include more explanation and examples of individual topics, such as criticality as applied for example to critical quality attributes and critical process parameters, design space and control strategy.

Part 1 and Part 2 of the ISPE PQLI Guide Series discuss the application of science, prior knowledge, and iterative use of quality risk management, as well as some of the underpinning processes and technologies, such as design of experiments, multivariate analysis, use of process analyzers, and process modeling.

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They make reference to case studies developed by PQLI® teams, especially the small molecule case study presented as an Illustrative Example as well as making reference to the many case studies in the public domain, (e.g., EFPIA Mock P2, Sakura, and ACE are small molecule drug product examples, and A-Mab is a monoclonal biotechnology drug substance and drug product example (References 2, 3, 4, and 5, Appendix 1). Compared with such case studies, more detail is given of the application of systematic, iterative, and different approaches to product and process understanding using quality risk management.

The concepts and examples developed reflect some of many optional approaches available to utilize QbD in pharmaceutical development and its effect on product realization.

1.2 Scope

The Series addresses practical implementation of the science- and risk-based approach throughout the product lifecycle as defined in ICH Q8(R2) (Reference 1, Appendix 1).

Product quality lifecycle implementation as the phrase indicates applies throughout the product lifecycle from product concept to routine manufacture, continual improvement, and ultimately product discontinuation. Parts of the Series address different activities in the product lifecycle. Parts 1and 2 focus on product realization using QbD. Other Parts address activities later in the product lifecycle, for example process performance and product quality monitoring system, change management, and selected elements of process validation

Science- and risk-based approaches may be used for development of drug substance processes and/or drug products of small molecules or biotechnological/biological products. ICH has commenced a topic, Q11 Development and Manufacture of Drug Substances (Reference 6, Appendix 1) (chemical entities and biotechnological/biological entities) which includes enhanced approaches to development of both large and small molecule drug substance manufacturing processes.

Conceptually, the principles of Q8(R2) (Reference 1, Appendix 1) also could be relevant to analytical method development and application.

The concepts in this Series apply to both new drug products and existing marketed products, and in line with Q8(R2) and Q11, Step 2, (References 1 and 6, Appendix 1) the Series has both drug substance and drug product examples. Since it is considered that the principles also apply to drug substance, there are discussion and examples of application of the science- and risk-based approach to drug substance (small and large molecule) process development, and continual improvement.

ICH terminology is used. Some phrases and concepts used in ICH guidelines, such as critical as applied, e.g., to critical quality attributes and critical process parameters, and design space as defined in Q8(R2) (Reference 1, Appendix 1), and control strategy defined in Q10 (Reference 7, Appendix 1) are judged to require further discussion and explanation to assist practitioners in their routine application and use. These are separate topics in Part 1, Product Realization using QbD: Concepts and Principles.

1.3 Benefits

Using the science- and risk-based approach should lead to deeper understanding of a product and its associated process or processes, which should lead to more robust and more efficient manufacture. In addition, this enhanced understanding also should reveal scientifically justifiable opportunities to propose flexible regulatory approaches and to obtain other business benefits.

A sound pharmaceutical development program has long been recognized as a pre-requisite for a high quality product. In recent years, both industry and regulators have realized the importance of designing the quality into products and processes. Quality cannot be tested into products: quality should be built-in by design.

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While a **minimal** – as opposed to enhanced – approach is still acceptable, there are many advantages to the employment of an enhanced, Quality by Design (QbD) approach, also referred to as a science- and risk-based approach. This approach includes the need for sound engineering input throughout, especially for design and control of pilot and commercial scale manufacturing processes, equipment, and facilities.

Therefore, this Guide Series is intended to assist industry in the development and implementation of pragmatic and practical "how to" approaches to product realization using the enhanced, quality by design approach supported by sound scientific, engineering, and business principles.

Part 1 and Part 2 of this Series, as well as subsequent Parts in the Series are intended also to stimulate internal considerations within a company during progression of a development or improvement project using the enhanced approaches, such as:

- how to organize a QbD project
- how to translate QbD principles and concepts described in ICH Q8(R2) (Reference 1, Appendix 1) to systematic development of products and manufacturing processes
- how to consider the impact of the QbD approach on the pharmaceutical quality system
- how to identify CQAs and CPPs
- how to assign levels of criticality
- how to describe Design Spaces
- how to describe the Control Strategy
- how to approach continual improvement having used QbD in development
- how to introduce real time release testing
- how to identify opportunities for proposing flexible regulatory approaches
- how to establish a process performance and product quality monitoring system
- how to establish and operate a change management system
- how to implement elements of process validation in line with FDA guidance

It is recognized that companies may wish to apply selectively elements of the science- and risk-based approach to product and process realization, based on their business strategy for a particular project. The enhanced approach could be applied to a greater extent, e.g., to some unit operations or it could be a business decision to perform more science- and risk-based studies post approval. This phased approach would mean that companies performed on a particular project a mixture or a range of enhanced and minimal approaches across what is a continuum of approaches.

Potential benefits are discussed in further detail in Topic I Overview.

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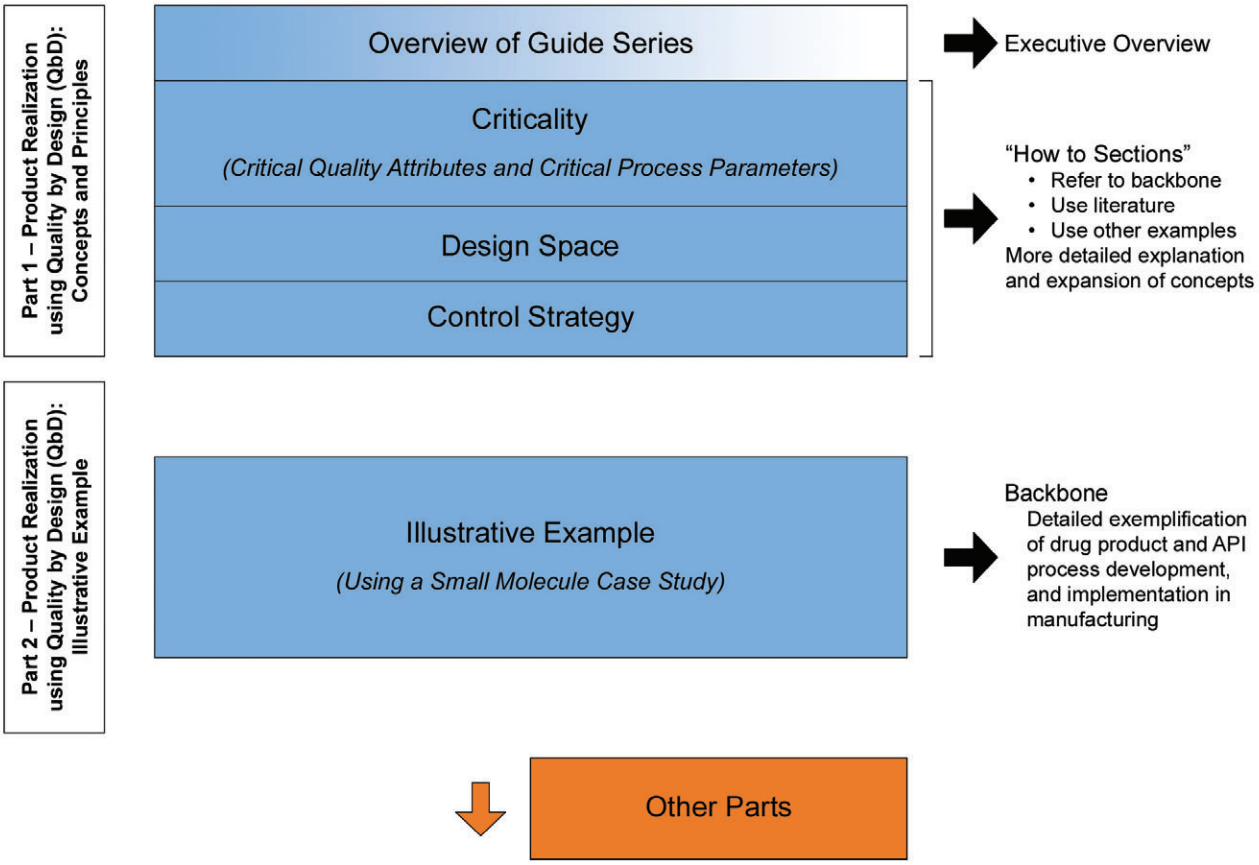
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2 Structure of the Guide Series, Product Quality Lifecycle Implementation from Concept to Continual Improvement

Topic I Overview summarizes the Guide Series and focuses on Part 1, Product Realization using QbD: Concepts and Principles and Part 2, Product Realization using QbD: Illustrative Example. It is intended to provide guiding principles and links to the greater detail and practical examples that are described in other topics, for example, in Part 1, Product Realization using QbD: Concepts and Principles and Part 2, Product Realization using QbD: Illustrative Example.

The relationship between Part 1, Product Realization using QbD: Concepts and Principles, Part 2, Product Realization using QbD: Illustrative Example, and subsequent Parts in the Series is shown in Figure 2.1.

Figure 2.1: Structure of Guide Series, Product Quality Lifecycle Implementation from Concept to Continual Improvement



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3 Product Realization using QbD

This Chapter discusses how to develop enhanced product and process understanding and how to use this enhanced understanding throughout the lifecycle of the product to the benefit of the company. These concepts are further expanded in sub-sections below.

The lifecycle of a pharmaceutical product is thoroughly illustrated in Q10 and briefly defined in Q8(R2) (Reference 1, Appendix 1) as:

"All phases in the life of a product from the initial development through marketing until the product's discontinuation."

Q8(R2) (Reference 1, Appendix 1) gives guidance on the flow from developing and defining Quality Target Product Profile to Continual Improvement.

This flow is represented in a schematic (Figure 3.1) developed by an EFPIA team (Reference 2, Appendix 1) of how the science- and risk-based approach can be progressed using Q8(R2) (Reference 1, Appendix 1) development concepts through the lifecycle of a product. While this figure focuses on the development of the drug product, the same principles apply to the development of the drug substance.

Figure 3.1: Conceptual Application of QbD through a Product's Lifecycle

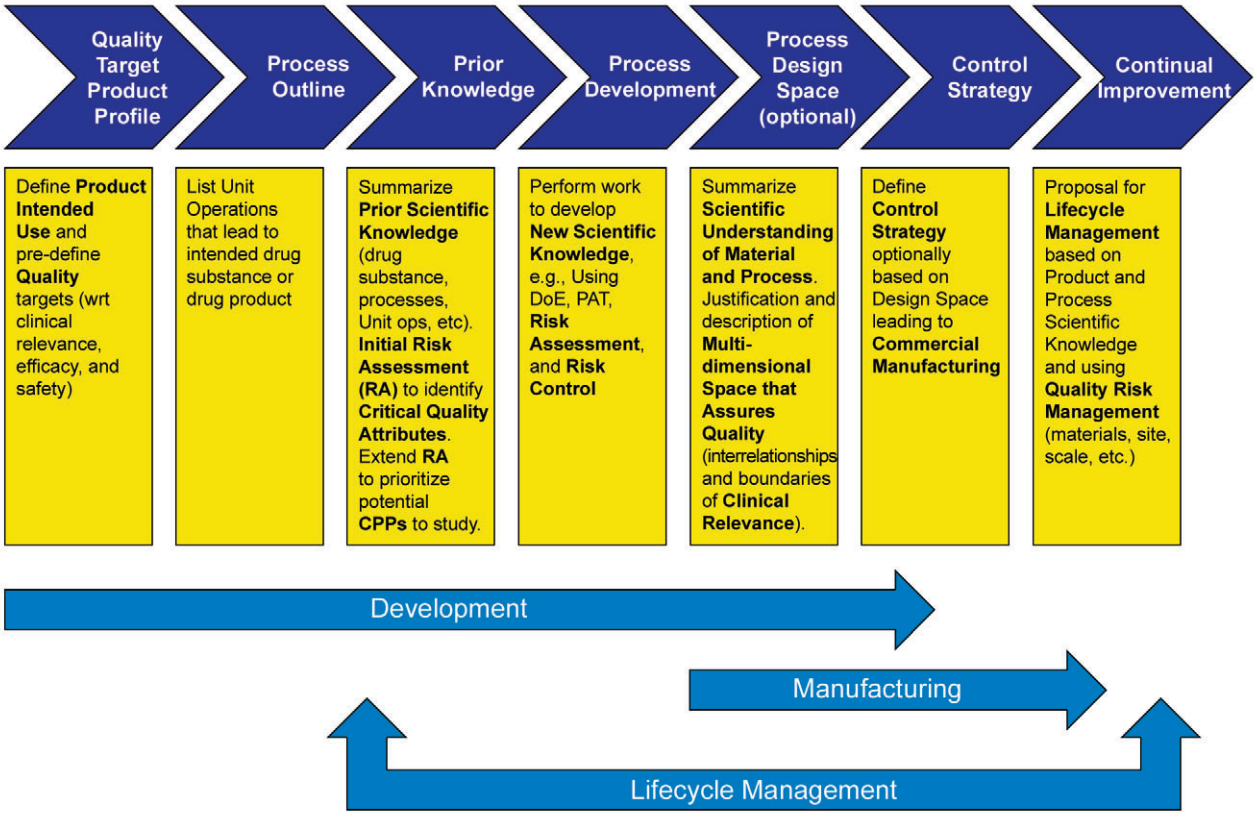


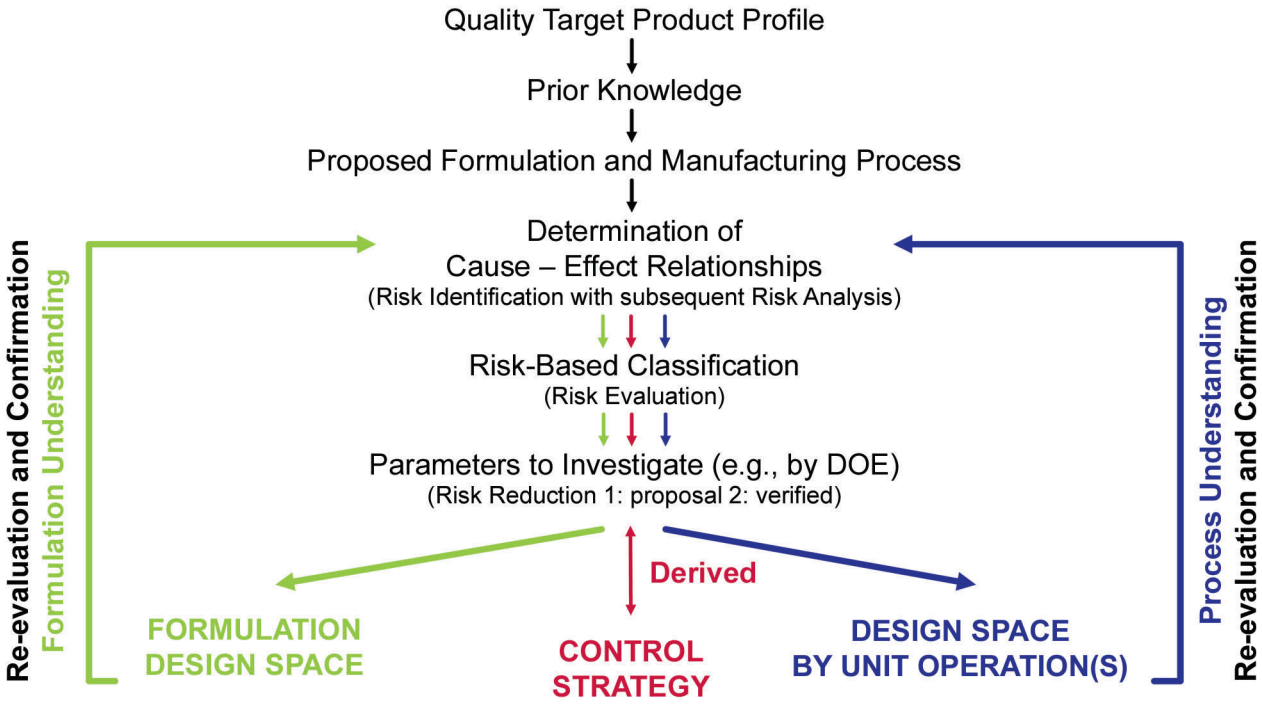
Figure 3.1 gives the impression that product/process development and continual improvement are linear processes. In practice, however, development and continual improvement processes may consist of several parallel activities and are typically iterative and the iterative nature is represented in Figure 3.2 as cycling arrows.

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Figure 3.2 shows the relationship between formulation and process development, this time in a vertical descending order, combined with the application of quality risk management as described in ICH Q9 (Reference 8, Appendix 1). More detailed explanation of the iterative nature of formulation and process development is given later.

Figure 3.2 is written for drug product, but the approach is equally applicable to drug substance. For some products, given a suitable outline manufacturing process, the formulation composition can be developed and optimized largely independent of the process variables and if considered desirable a formulation design space could be proposed. For many products and certainly for complex products, it is probable that formulation and process factors are studied in combined experimental designs. In some cases, there is iteration between the intended or evolving control strategy and experimental studies. The iteration between an evolving control strategy and experimental studies is represented by the double-headed arrow to and from "control strategy."

Figure 3.2: Iterative Approach



As a further attempt to explain the science- and risk-based approach to product realization, Figure 3.3 shows the QbD flow horizontally as a series of deliverables and some actions with the major over-arching principles applying to all steps, such as science, quality risk management, and knowledge management above this flow, these latter two principles being considered enablers in Q10 (Reference 7, Appendix 1).

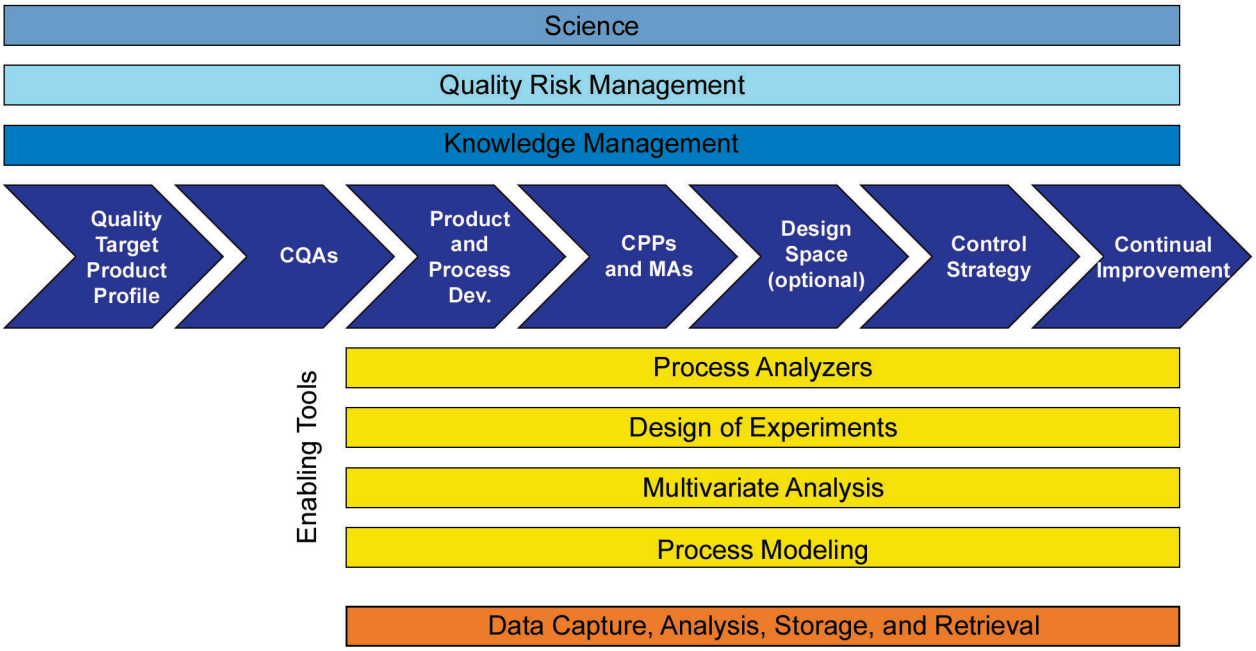
Some of the technology enablers as discussed in FDA PAT Guidance (Reference 9, Appendix 1) are shown supporting this approach, and these could be applied during product and/or process development. Additionally, based on the outcome of development studies, some of these tools could be applied in the control strategy, and during routine manufacture as well as being tools to assist in continual improvement, e.g., as part of the process performance and product quality monitoring system.

Underpinning all these activities in a computerized environment are the steps of data capture, analysis, storage, and retrieval. In the interests of clarity and simplicity, many other concepts such as change management and management review are omitted from Figure 3.3.

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Figure 3.3: QbD Approach showing Overarching Principles and some Enabling Tools



In summary, and as shown in Figure 3.1, a Quality Target Product Profile (QTPP) is proposed, which is a defined (Reference 1, Appendix 1) as:

"A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product."

During development of a new product, the QTPP could evolve and be refined as the project development process progresses. For example, when developing a simple tablet, the strength(s) to be submitted and included in a QTPP may not be finalized until after completion of Phase 3 clinical studies. A QTPP could be considered a qualitative and quantitative description of the design goal. Based on the QTPP an initial product and manufacturing process is proposed perhaps with several options, which may require experimental data coupled with risk management to make decisions among options. Company strategy, prior knowledge, and experience of a process or availability of equipment and facilities also could influence the choice of manufacturing process.

Prior knowledge could be used first in a risk management exercise to produce a list of potential Critical Quality Attributes (CQAs) and to prioritize this list based on risk ranking using harm to the patient or severity. Prior knowledge also may be employed in another risk management exercise, e.g., using Failure Mode, Effects, and Criticality Analysis (FMECA) to identify process parameters and Material Attributes (MA) which could impact potential CQAs and rank the risk of these process parameters and MAs impacting a potential CQA using a combination of severity, probability, and detectability. This risk ranking also could be used to prioritize the study of those potential Critical Process Parameters (CPPs) and MAs which may impact potential product CQAs.

An initial list of potential product CQAs could be modified as development progresses to produce the final list of CQAs. For example, at the start of development of a controlled release product, quantitative in vitro drug release acceptance criteria and selection of an appropriate dissolution medium are frequently not known. These are often developed in parallel with development of the formulation.

Risk assessment could be applied iteratively to select and prioritize factors to study in a systematic manner, usually in statistically-designed experiments. Output from these studies can optionally be summarized in a design space. Risk management also should be used to aid establishment of a control strategy or control strategy options.

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Following introduction of commercial manufacture of the product, opportunities for appropriate improvements to process performance and/or product quality could be identified from, e.g., the process performance and product quality monitoring system or the Corrective Action and Preventative Action (CAPA) system, and changes made using the change management system. This continual improvement process is iterative throughout the lifecycle of the product.

Technical and business processes companies could consider to effect continual improvement of process performance and product quality, whether the product was originally developed using science applicable at that time or a science- and risk-based approach, are given in the JPI paper, *Application of Science- and Risk-based Approaches (ICH Q8, Q9, and Q10) to Existing Products* (Reference 10, Appendix 1). In summary, however, as shown in Figure 3.1, opportunities for continual improvement in product or process would cycle back to the existing state of knowledge.

Continual Improvement of Process Performance and Product Quality (shortened to Continual Improvement in this Guide Series) are described in Section 3 of ICH Q10 (Reference 7, Appendix 1). Section 3 (ICH Q10) is split into two parts, 1. Lifecycle Stage Goals, which is a summary of the product lifecycle stages and 2. Pharmaceutical Quality System Elements (PQSE), which has more detail for manufacturing operations.

The PQSE is made up of the following four sub-parts:

- Process Performance and Product Quality Monitoring System
- Corrective Action and Preventive Action (CAPA) System
- Change Management System
- Management Review of Process Performance and Product Quality

Control Strategy is discussed as part of the Process Performance and Product Quality Monitoring System Section (ICH Q10).

The following sections of this Guide provide increased detail and more considerations compared with the above summary. They describe the EFPIA flow of how to implement Q8(R2), Q9, and Q10 (References 1, 7, and 8, Appendix 1) for practitioners developing products and processes, performing scale-up, technology transfer, and engaging in commercial manufacturing.

These suggestions must not be considered the only way to apply science- and risk-based approaches, nor should they be considered as regulatory guidance. As an example, companies have options to develop product and process understanding in different ways and use this understanding to propose control strategies without describing a design space, as indicated in Appendix 1 of Q8(R2) (Reference 1, Appendix 1).

More detailed description of science- and risk-based steps is given in the following sections and further explanation and alternative approaches are given in other topics in Part 1: Concepts and Principles and in Part 2: Illustrative Example.

3.1 Quality Target Product Profile

The Quality Target Product Profile (QTPP) for a new product at the start of its development is likely to be qualitative or semi-quantitative and be reflective of the needs of the patient and user. A QTPP for an immediate release solid dosage form being designed to have defined clinical, safety, and efficacy objectives, e.g., relating to patient population, indication, or dose regimen is shown in Table 3.1.

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Table 3.1: Initial Quality Target Product Profile for an Immediate Release Tablet

Product Attribute	Target
Description	Round, coated convex tablet with size being patient acceptable
Identity	Positive for active ingredient
Assay	+/- 5% x mg and/or y mg, the doses in a Phase 3 study
In Vivo Availability	Immediate release determined by in vitro dissolution test
Degradation Products	Meet criteria of Q3B (R2)
Uniformity of Dose	Meets pharmacopoeial criteria
Microbiological Limits	Meet pharmacopoeial criteria
Container	Stable in multiple dose and unit dose packs. Packaging materials to be determined

For a once-a-day oral controlled release dosage form, the QTPP could be similar to above with the differences shown in Table 3.2.

Table 3.2: Alternative *in vivo* Criteria for an Oral Controlled Release Dosage Form

Product Attribute	Target
In Vivo Availability	Assured by extended release in vitro test

A comprehensive QTPP for a monoclonal antibody drug product is given in Table 3.3 (taken from Table 5.2 from the A-Mab Case Study (Reference 5, Appendix 1)), which reflects considerable prior knowledge.

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Table 3.3: Quality Target Product Profile for A-Mab Drug Product

Product Attribute	Target
Dosage Form	Liquid, single use
Protein Content per Vial	500 mg
Dose	10 mg/kg
Concentration	25 mg/mL
Mode of Administration	IV, diluted with isotonic saline or dextrose
Viscosity	Acceptable for manufacturing, storage, and delivery without the use of special devices (e.g., less than 10 cP at room temperature).
Container	20R type 1 borosilicate glass vials, fluro-resin laminated stopper
Shelf Life	≥ 2 years at 2 to 8°C
Compatibility with Manufacturing Processes	Minimum 14 days at 25°C and subsequent 2 years at 2 to 8°C, soluble at higher concentrations during UF/DF
Biocompatibility	Acceptable toleration on infusion
Degradants and Impurities	Below safety threshold or qualified
Pharmacopoeial Compliance	Meets pharmacopoeial requirements for parenteral dosage forms, colorless to slightly yellow, practically free of visible particles and meets USP criteria for sub-visible particles
Aggregate	0 to 5%
Fucose content	2 to 13%
Galactosylation (%G1 + %G2)	10 to 40%
HCP	0 to 100 ng/mg

Many of the attributes in Table 3.3 can be refined, e.g., by selection of dose from clinical studies and can have more quantitative targets as development progresses and associated methods are developed.

There also could be characteristics of the product important to the company, such as measures designed to assure security in the supply chain following drug product manufacture, e.g., anti-counterfeiting measures. Strictly these criteria are not part of a QTPP as defined in ICH; however, these could be additional development goals when scoping out a project.

3.2 Product and Process Outline

Based on the QTPP, an initial product and process outline should be proposed based either on preliminary studies, which may not be very extensive, or on company experience and commercial strategy, which should consider previous products and knowledge, manufacturing equipment, and available facilities. For example, many companies have **platform technologies** which they prefer to use, e.g., dry granulation using roller compaction, which bring many advantages to the company from prior knowledge from other products as well as efficiency of development and commercial manufacture.

If it is an innovative product or process, much preliminary experimentation may be required:

- to propose a potential product and process to optimize

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- to understand potential CQAs by developing better estimates of initial acceptance criteria
- to possibly modify the initial list of potential CQAs

3.3 Prior Knowledge

At the start of development of a product or process using QbD, risk assessment in conjunction with prior knowledge should be used to establish the initial list of potential CQAs and any associated acceptance criteria. Prior knowledge can come from the literature, company experience, an individual's experience, or previous work on this project, e.g., drug substance characterization and previous formulation work to support toxicological or early clinical studies.

Other examples of prior knowledge are use of platform technologies as introduced above, e.g., roller compaction or high shear wet granulation where a company benefits from predicting potential CPPs from these unit operations using its extensive prior knowledge of previous products and processes.

In summary, prior knowledge and risk assessment are used to derive a list of potential CQAs and material attributes and potential critical process parameters to study.

3.4 Product Critical Quality Attributes

Critical Quality Attributes (CQAs) of the product could be considered a more quantitative representation of the QTPP. A CQA is defined in Q8(R2) (Reference 1, Appendix 1) as:

"A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality."

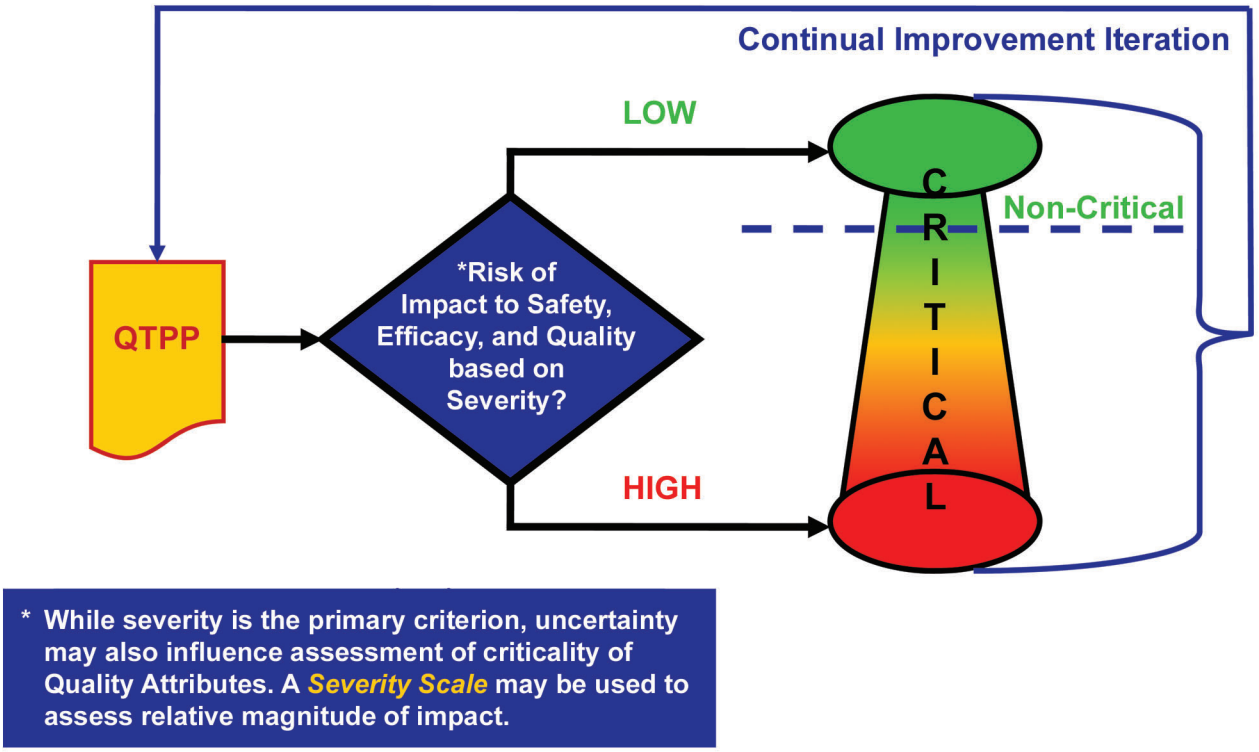
Discussion of their derivation from development work is given in Q8(R2). The iterative nature of product and process development requires that attention is given as early as possible in development to refine from the QTPP the initial list of potential product CQAs and to move toward the proposed list of critical product QAs, establishing acceptance criteria for those attributes deemed **critical**.

The initial list of quality attributes can be prioritized for subsequent evaluation primarily or solely on the magnitude of severity of the risk of harm to the patient. Probability, detectability, and uncertainty may all change with increased understanding. However, severity of impact is unlikely to change regardless of increased understanding. For this reason, severity and uncertainty are the important factors for assessing the criticality of product quality attributes as shown in the process represented in Figure 3.4 as one example of determining risk ranking to assist development. In Figure 3.4, **uncertainty** is a risk factor to consider when there is not a clear relationship between a potential CQA and harm to the patient.

The concept of **uncertainty** is extensively discussed in the A-Mab Case Study (Reference 5, Appendix 1) where scoring criteria for uncertainty are suggested. Some companies developing small molecules include **uncertainty** in the severity risk scale rather than having it as a separate factor. Using this qualitative ranking of **severity of harm to the patient** produces a range of risk values. For example, non-sterility of an injectable product could have a very serious and life-threatening impact on the patient and have a high risk score. It is possible that a minor deviation of pH from **ideal** for the same product may have less severe consequences, perhaps of minor, maybe hard to detect difference in pain at the point of injection and a lower risk score.

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Figure 3.4: CQA Decision Tree Analysis



This range of risk values can be used to prioritize allocation of resources to try to increase understanding, if possible, of the impact of a potential CQA on the patient, and also to prioritize resources given to understanding the impact of material attributes and process parameters on a particular product CQA. Since the quality attributes of a product may be linked to or influenced by specific input variables of the manufacturing process, i.e., process parameters and material attributes, a functional relationship between product quality attributes and material attributes and process parameters may be established. Evaluating this relationship increases process understanding and product knowledge which can ultimately identify opportunities to reduce risk.

CQAs of a drug product are likely either to be included in the finished product specification or to be functionally related to the finished product specification.

Table 3.4 gives an example of a potential relationship between QTPP, potential CQAs, and CQAs for degradation products for an immediate release solid dosage form. At the beginning of drug product development, understanding of drug substance is usually well known; however, knowledge of the degradation of the product increases as development progresses.

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Table 3.4: Example Relationship between QTPP and QAs at Beginning and End of Development

QTPP	Potential CQAs at Beginning	CQAs at End
Degradation Products meet Q3B (R2) criteria	Impurity 'z' meets 0.8%, the level initially qualified in animal toxicity studies. 'z' is a synthetic impurity as well as proposed as a very unlikely degradation product from stress analytical development studies of drug substance in solution at 80°C. Impurity 'w' meets 0.5%, the level qualified in toxicity studies. 'w' is found in drug substance accelerated stability studies and is a drug substance degradation product and a potential drug product CQA.	Impurity 'z' is not a degradation product since no increase in long term, accelerated, or stress stability studies in drug product and no increase in accelerated drug substance studies. It is **not a degradation product CQA.** It is a drug substance impurity CQA. Level of **'w' is a CQA** since it increases in drug product accelerated and long term stability studies, but to less than 0.5% within the proposed shelf life.

In Table 3.4, potential degradation product "z" is not a CQA arising from drug product manufacture and storage since studies show it is not a degradation product found under stress, accelerated or long term storage of drug product and accelerated and long term storage of drug substance. This is an example where increased understanding has changed the "uncertainty" rating of a potential CQA from "it could be" a degradation product to it is not a degradation product. Impurity "z" still has potential for "harm" to the patient and as such is a CQA for drug substance as impurity from synthesis of the drug substance. Impurity "z" should be controlled as a synthetic impurity at an appropriate level. Degradation product "w" is a drug product CQA as its level increases during storage of the product and it is important to ensure that its level does not exceed the acceptance criterion of the specification. This example is equally applicable to both a small molecule and a biotechnological molecule.

3.5 Product and Process Development

Development of products and/or processes using the science- and risk-based approach is a very large topic and beyond the scope Topic I Overview. The approaches to development, timelines, and processes that companies use are different. Each product is different and the process of obtaining regulatory approval and post approval lifecycle management is unique even when a company has considerable prior knowledge. The capabilities of companies, levels of technical expertise and skills, and organizational objectives are also different.

However, detailed examples of science- and risk-based approaches as summarized in Topic I Overview are expanded in Part 2: Illustrative Example as applied to a small molecule tablet manufactured by direct compression.

Development of formulations and processes for all dosage forms should follow the same principles although details will obviously differ. The application of science- and risk-based approaches, as described in Figures 3.1, 3.2, and 3.3, shows the importance and continuing need to apply science, quality risk management, and knowledge management throughout development and in the organizational processes. Application of QbD can benefit from careful consideration of the following:

- objectives of work
- multi-disciplinary working
- scale of work
- study designs

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- iterative nature of product and process development
- use of Process Analytical Technology (PAT) tools
- linking material attributes and CPPs to CQAs
- knowledge management

These aspects are considered in the following sub-sections.

3.5.1 Objectives of Work

Practitioners should be very clear regarding objectives of their development work, which should be described in a project scope. For product realization, the needs of the patient are paramount, but the requirements of the health care professional, regulatory authorities, and internal customers also should be considered.

The quality attributes of purchased materials and components (the material attributes) should be well understood, and the robustness of the supplier quality management system should be confirmed (e.g., a change management system to adequately evaluate and communicate changes) to ensure critical material attributes remain within required and agreed acceptance criteria.

The quality objectives of the project should be documented in the QTPP. The company also should be clear what it is intending to achieve from a business perspective. Risk management tools, as described in Q9, can be used to the benefit of the project to rank for the company the importance of both quality and business objectives. The business objectives may include:

- development of robust process
- establishment of an efficient control strategy
- perform work within a set timeframe
- meet process safety requirements
- meet worker protection requirements
- meet environmental requirements
- obtain some desired flexibility due to business uncertainties, such as volumes for manufacture, requiring flexibility of scale, site and equipment, potentially using a design space approach
- optimize movement of product through the manufacturing part of the supply chain
- work within resource or cost constraints

Use of Integrated Project/Program Management, Six Sigma and/or Lean Manufacturing (Reference 11 and 12 Appendix 1), and PAT tools could help structure this work. For example, Design for Six Sigma (Define, Measure, Analyze, Design, Verify) offers a structured approach to identify impact to quality attributes and potentially their associated risk mitigation, determine cause and effect relationships through first principle understanding and/or DOE, optimize design space, and demonstrate compliance and capability.

Design for Six Sigma and Lean manufacturing tools deployed during product development are intended to enable a systematic approach (such as QbD), resulting in lower overall cost both during development and routine manufacturing. For many companies and projects, the iterative approach to application of risk management and safety design could evaluate both quality and business requirements in parallel with each other.

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The company's development project team and its management should establish a systematic process to address these objectives and any constraints.

There are options and choices here for companies and teams when applying the science- and risk-based approach, such as deciding how much work should be performed pre-approval. There are opportunities to do some of the work post-approval as part of continual improvement.

There may be benefits for companies and teams to develop products and processes destined for commercialization with a science- and risk-based approach. However, all the desired business objectives may not be achieved at initial approval. See Chapter 5 of Topic I Overview for further discussion of benefits.

A key objective is to obtain a good understanding of the product and process and determine not only which material attributes and process parameters are important in terms of impact on CQAs and ultimately may be critical, but also what factors are much less or *not* important. For these less important factors, it should be relatively easy to apply quality risk management and propose that changes to these factors could be considered and justified using the company quality management system. An objective will be to derive quantitative relationships between CPPs and relevant material attributes and CQAs, these being derived from experimental studies leading to an efficient control strategy.

3.5.2 Multi-Disciplinary Working

An integrated multidisciplinary approach should be taken with product and process development, as scale-up, manufacturability, and regulatory issues may be identified early in the project lifecycle. This allows for more robust project planning and ensures end user requirements are addressed from the outset. For multinational companies, it may be necessary to consider different national and regional requirements, and to include people from different sites.

3.5.3 Scale of Studies

Companies should decide on the appropriate scale of studies, but generally it is more efficient to use the smallest scale practical, taking account of relevance of results to eventual scale(s) of manufacture. Use of the smallest scale optimizes use of materials and generally gives most rapid turn round of results, and again quality risk management could be used to assist in making decisions regarding which scale to use.

When developing products and processes for new products incorporating new drug substances, drug substance is often in very short supply and there is the additional challenge of balancing use of material for process development studies, especially at large scale, and supplying clinical programs.

Many relationships are scale independent or evident from the initial science, e.g., those with a thermodynamic basis, and for others, such as rates of reaction, scale dependence is relatively easy to explain. In other cases, science could be used to explain and document scale effects, and in yet others, it may be necessary to perform studies at different scales to either confirm or further develop relationships and scale up factors.

The process operating in manufacturing should always be validated and in a state of control. The design and extent of studies to confirm that the process is operating in this state of control depends on the science, the amount of understanding that has been achieved, and the risk profile of the process when it is introduced into manufacturing.

The technology transfer step from R&D to Manufacturing in the conventional way of working is changing and is likely to move from a prescriptive method of performing technology transfer and/or manufacture of a fixed number of batches to a series of confirmatory studies based on the level of understanding and the level of risk. As a consequence of these structured studies, it is expected that the number of troubleshooting exercises due to unexpected causes should be significantly reduced compared to the conventional way of working.

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3.5.4 Study Designs

For optimum use of time, equipment and materials as well as greater assurance that results will be of greatest value, experiments should be designed carefully. Since it must always be assumed until proven otherwise that product and process development are multi-factorial, experimental plans should use a formal statistical design, called Design of Experiments (DoE). There are many possible designs and choice depends on the situation. The project team should include not only persons skilled in the scientific definition and execution of study objectives, but also persons skilled in formal statistical experimental design, data evaluation, and data interpretation. If using statistical and scientific execution skills in different individuals, the development scientist will generally be responsible for the control of the experiments and work with the statistician who will assist with design, and advising on limitations and confidence intervals of results. Further references are given in Appendix 1 of this Overview.

The conventional univariate approach is unlikely to pick up the dependencies between variables, such as material attributes, CPPs, and CQAs, and impossible for it to determine interactions between variables. In the case of some complex products or processes, the univariate approach may make the product or process impossible to develop or leads to unnecessarily fixing variables in ranges, which when all are fixed, may make the product very difficult or impossible to manufacture without significant batch rejects. In effect, it would be more by chance that a satisfactory batch was produced in this worst case. However, a univariate approach is useful when performing early screening studies, and obviously when relationships are themselves univariate.

3.5.5 Iterative Nature of Product and Process Development

It is highly unlikely that one experiment or even one series of well-designed experimental plans will give all the required outputs. In quality risk management terms, conducting development work is risk reduction, part of risk control, and the output from studies should be evaluated in either a formal or an informal risk acceptance step to decide whether results allow a risk to be accepted, i.e., there is sufficient confidence that the risk is low or that the risk is still high and then there are further options.

The further options are to accept the risk, which will probably lead to a robust control being applied, or to perform further studies to develop more understanding with the objective of reducing the risk to an acceptable level. A schematic of this iterative process for development of a drug product linked to the risk management steps is given in Figure 3.2.

It is unlikely that **severity** of impact of a CQA on the patient will be changed from formulation and process design and optimization studies; the risk will be reduced by decreasing the **probability** that CQA acceptance criteria will not be achieved (increasing the probability the a CQA acceptance criteria will be achieved) and/or by increasing the **detectability** of failure.

For some simpler products and processes, it may be possible to design the product formulation then optimize the process. Process optimization could involve investigating the whole manufacturing chain or investigating each unit operation on its own, looking at inputs to and from that unit operation (feed forward and feedback). This is a choice for the development team. For complex products, design of the formulation in terms of quantities and material attributes of excipients could depend on and interact with process parameters employed in the process, as well as influence variability. Only formal design of experiments will estimate the dependencies and variability, and inform if there are interactions between factors studied.

3.5.6 Use of PAT Tools

Since pharmaceutical processes are dynamic, it is desirable – but not essential – to develop enhanced understanding of processes using real time analytical tools as well as to use some of these analytical tools to improve detectability scores in risk ranking exercises. There are many analytical, data analysis and modeling, and experimental design tools that could be employed and technology is changing and advancing rapidly, and practitioners are referred to appropriate specialist meetings or societies for the latest information.

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FDA PAT Guidance (Reference 9, Appendix 1) discusses PAT tools. In addition, information relating to PAT implementation in the European regulatory environment can be found on the EMA Web site (Reference 13, Appendix 1). Standards for developing processes using PAT have been developed by consensus by teams working for the American Society for Testing and Materials (ASTM) (Reference 14, Appendix 1).

The PAT toolbox consists of multi-factorial tools for design, data acquisition and analysis, process analyzers, process control tools, and continual improvement and knowledge management tools, and these are placed in perspective in Figure 3.3. These PAT tools can be applied in development studies, especially at smaller scale to speed up the development by delivering real-time data relating to understanding and/or measurement of processes and the results of their application should make scale-up issues easier to deal with.

PAT tools also can provide important input to arrive at a mechanistic understanding, e.g., of chemical transformations, and also provide some insight as to the need for additional control. Then based on the established process understanding, decisions can be taken aided by quality risk management regarding which of these tools should be employed on production scale and in the control strategy (Reference 7, Appendix 1). An efficient and effective control strategy is a goal of the science- and risk-based approach and this is discussed further in Section 3.7 and Topic IV Control Strategy. If a control strategy includes some form of automated control system, the use of PAT tools is likely to be essential.

In addition to use of analytical and data analysis tools, practitioners need to consider the implications of data capture, storage, and retrieval, which is beyond the scope of this document. There also should be an understanding that data need to be summarized and conclusions drawn as information and knowledge, and it is usually summarized data and information which are included in submissions and used as input into a subsequent risk assessment process in the iterative development cycle.

3.5.7 Linking Material Attributes and CPPs to CQAs

It is expected that there will be relationships between one or more material attributes, which could be called critical quality attributes of a starting material, excipient, intermediate (in process material, e.g., output from a unit operation), and/or one or more Critical Process Parameters (CPPs) and product CQAs.

Figure 3.5 illustrates in a flow chart how from development studies, the functional relationship of CPPs (PP1, PP2, etc.) impact on a CQA. These relationships often also include material attributes and they can be used in developing a design space, as given in the design space definition.

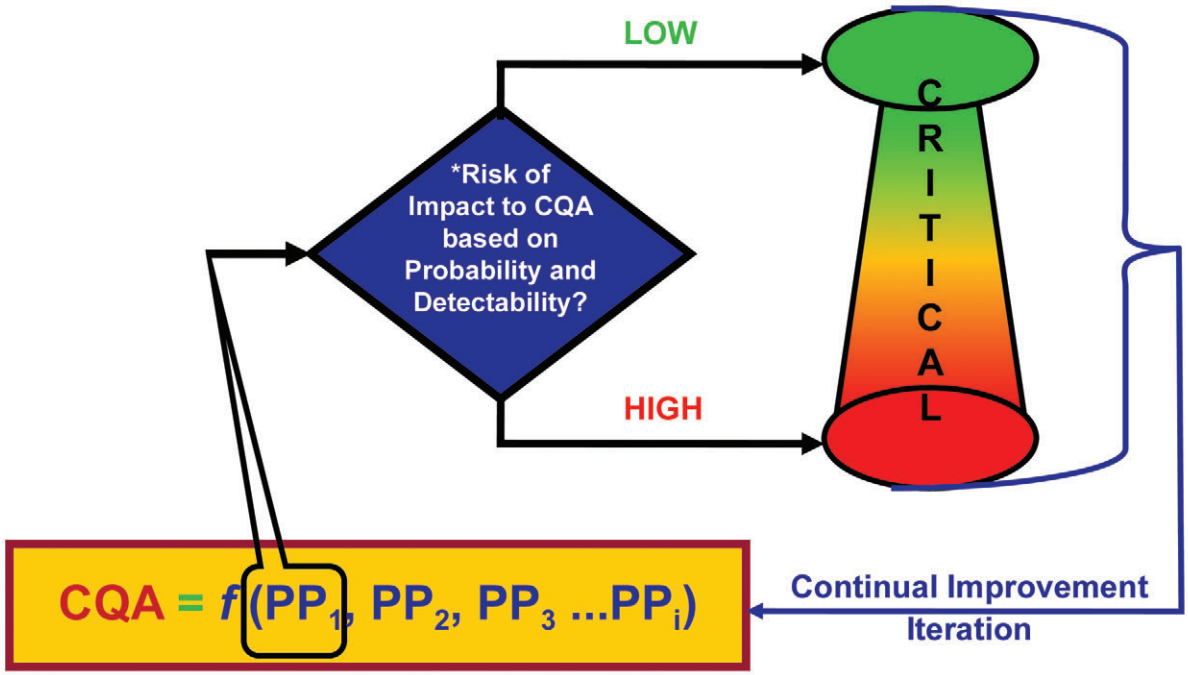
A Critical Process Parameter (CPP) is defined in ICH Q8(R2) (Reference 1, Appendix 1) as:

"A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality."

From development studies, variability of a particular process parameter or material attribute can be estimated and from this variability estimate, probability of meeting CQA acceptance criteria can be estimated.

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Figure 3.5: Critical Process Parameter Decision Tree



* While probability and detectability are the primary criteria, severity may also influence assessment of criticality of Process Parameters and Material Attributes in accordance with a classical RPN exercise.

Studies also should demonstrate how a material attribute or CPP could both directly or indirectly be measured and controlled. The risk assessment of material attributes or potential CPPs should result in a **continuum** of level of importance of both the attributes and parameters which would lead to different levels of importance being attached to levels of monitoring and/or measurement in a control strategy.

For example, a CPP which has a high probability of causing failure relative to its relationship to a CQA could require monitoring using a method with appropriately low variability, and potentially with feedback to assure that processing produces acceptable output. This CPP and how it is controlled also could engender additional justification in a regulatory submission. A critical parameter with low probability that its variability would impact on a CQA would have lower criticality, and therefore, could require much less discussion in a regulatory submission particularly when it impacts on a less critical CQA. Conversely, a less critical CPP impacting on a highly critical CQA may require significant attention and discussion in a regulatory submission and cannot be ignored.

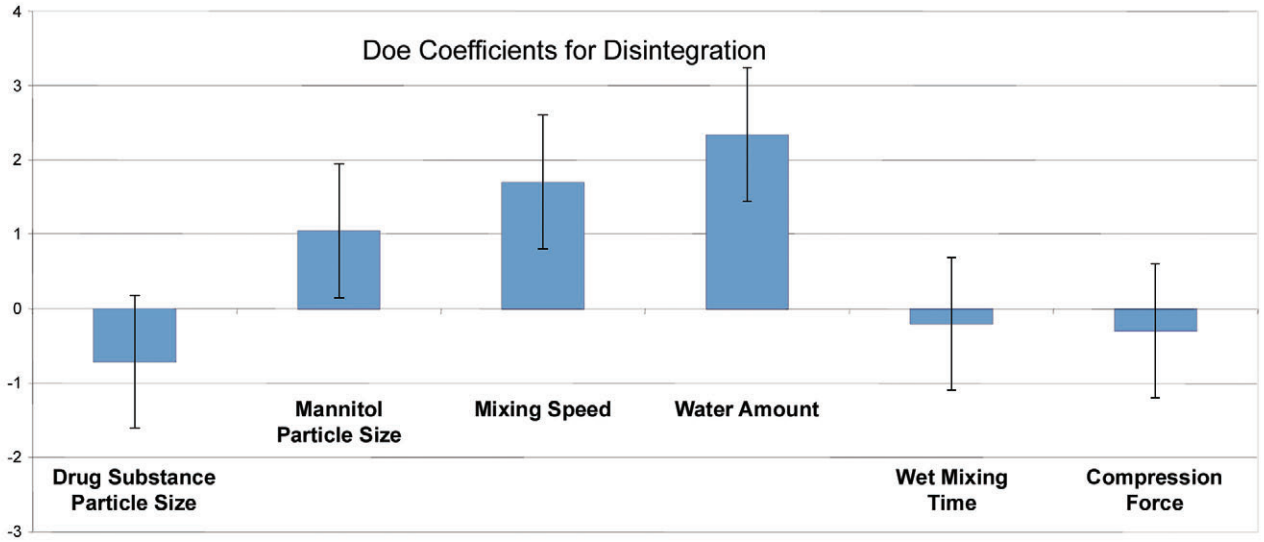
A less critical process parameter also may be readily detectable through some quantifiable measure and this reduces further its impact on a CQA. This continuum is demonstrated in Figure 3.6, taken from the EFPIA Mock P2 presentation (Reference 2, Appendix 1), which shows the relative importance of some process parameters and a material attribute (drug substance particle size) on the CQA, disintegration as output from a partial least squares model resulting from DoE studies.

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Figure 3.6: Process Development

Relative Importance of Process Parameters on Disintegration could be derived from evaluation of Coefficient Plot from Partial Least Squares (PLS) Model (Data out of DoE studies)



It can be seen from Figure 3.6 that water amount, mixing speed, and mannitol particle size are statistically significant, as their error bars do not cross zero. This, along with the size of these coefficients, indicates that these inputs (factors) have an effect on disintegration and may be critical. The control strategy needs to take account of these findings. Alternatively, wet mixing time, compression force, and drug substance particle size, have relatively small coefficient estimates. They also have error bars that cross zero indicating that these inputs are not statistically different from zero. Therefore, these inputs are not critical in this example. Assigning the relative importance to material attributes and process parameters assists in designing the control strategy.

From results of development studies and after applying quality risk management, companies have to summarize and justify what quality attributes and process parameters (and material attributes) are judged critical.

Further discussion of assignment of criticality for CQAs and CPPs is given in Topic II Criticality and in Part 2: Illustrative Example.

3.5.8 Knowledge Management

An important outcome of the science- and risk-based approach is managing the totality of data, information, and knowledge produced, covering variables not only which are important, but also those which are not.

Development and continual improvement work are ongoing processes, which will produce new data, with potentially new knowledge or understanding, and these also have to be managed. Traditionally, knowledge is summarized in written reports, which could be stored and filed electronically with raw data increasingly being stored in computerized systems. The mechanisms to capture, store, and access data stored electronically is beyond the scope of Parts 1 and 2 of this Guide Series.

Additionally, there are also some electronic systems, e.g., **expert systems** for storing and retrieving knowledge and e-laboratory notebooks for recording data and observations, and it is probable that these will evolve and improve in the future. As a process for managing knowledge, some companies have introduced product stewardship roles with a responsibility to manage knowledge across the product lifecycle.

Managing knowledge across the R&D and manufacturing boundaries and throughout the product lifecycle is a complex subject that is evolving through use of new business processes and technology.

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3.6 Design Space

Design space is defined in ICH Q8(R2) (Reference 1, Appendix 1) as:

"The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality."

The output from enhanced understanding work can be summarized in a design space as discussed in Q8(R2) leading to opportunities to propose more flexible regulatory approaches since working within design space is not considered a change. Movement outside design space is considered a change and would normally initiate a regulatory post approval change process, which is region-specific.

It is not essential to propose a design space. A conventional approach is still acceptable and it is highly unlikely that a design space could be proposed if a conventional approach had been used. However, there are benefits of proposing a design space. For example, justifying regulatory flexibility as discussed in Q8(R2) (Reference 1, Appendix 1) should be easier if a design space is proposed and well justified.

Design space is established from experimentation. However, the boundaries may be established using risk management. Boundaries could be based on quality attributes of materials and critical process parameters which are scale- and equipment- independent, which should make changes of scale and equipment easier.

When performing development studies, it is not necessary to find the **edges of failure** for the design space, as this may involve significant unnecessary experimental work and cost. Thus, a design space boundary may not represent an **edge of failure**, the design space region being the **experimental space** studied. If the **experimental space** studied does find an **edge of failure**, it is unlikely that a company would choose the edge of failure as a design space boundary, probably using statistical tools to help select the boundary. A design space could based on first principles science or an empirical relationship derived from data from, for example, DoE studies, or it could be a relationship in the continuum between first principles science and an empirical relationship. Design space represents the output from:

- multi-factorial process understanding
- multi-factorial process models, ideally based on physical, chemical, and/or engineering fundamentals
- multi-factorial experiments

Where a design space is proposed, the control strategy should ensure that a product of the required quality is produced consistently through operation within that design space.

Output from development studies aimed at developing a design space should determine less important material attributes and process parameters (i.e., non-critical) where there also should be opportunities to propose regulatory flexibility.

Examples of presentation of design space are given in Appendix 2 of ICH Q8(R2) (Reference 1, Appendix 1) and other examples are given in Topic III Design Space and Part 2: Illustrative Example.

Using Figures 1c and d in Appendix 2 of ICH Q8(R2) (Reference 1, Appendix 1) as the basis of an example (re-presented as Figures 3.7 and 3.8), in the idealized example the full design space is represented by the whole light surface in Figure 3.7 as a non-linear function. It would need to be represented by an equation. Alternatively, a "squared off" design space could be proposed by using the ranges represented by solid black square as in the original Figure 1d in ICH Q8(R2) (see Figure 3.8).

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Figure 3.7: Design Space for Granulation Parameters, Defined by a Non-linear Combination of their Ranges that Delivers Satisfactory Dissolution (i.e., >80%)

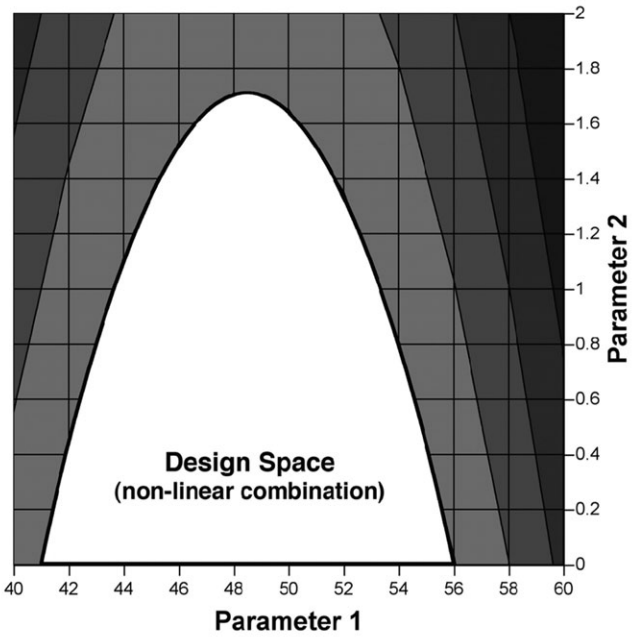
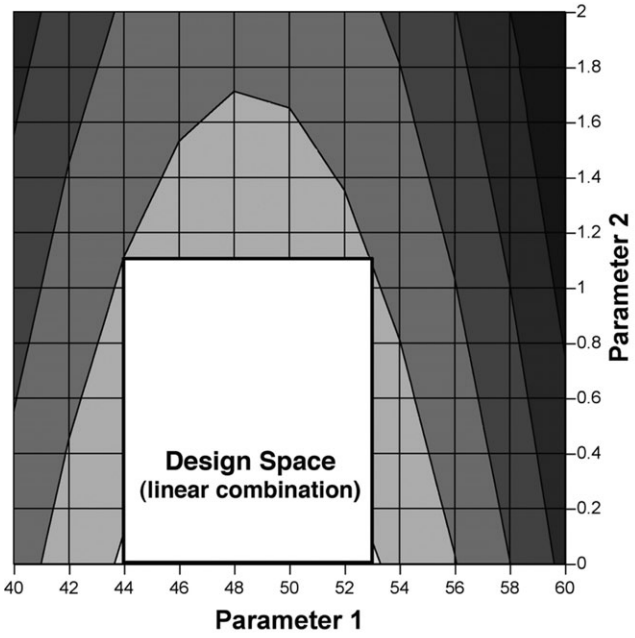


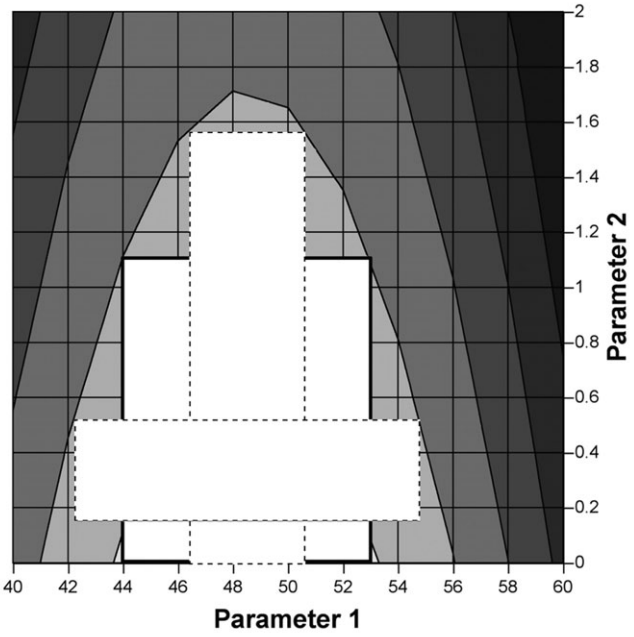
Figure 3.8: Design Space for Granulation Parameters, Defined by a Linear Combination of their Ranges that Delivers Satisfactory Dissolution (i.e., >80%)



Using the **squared off** section, a portion of the design space is "thrown away," but the benefit is in the simplicity of the representation. Other rectangles can be drawn within the design space depicted in Figure 3.7, there being multiple combinations of "squared off" ranges that could be chosen as the design space as shown by squares with dotted lines; see Figure 3.9. Exact choice of which parameter to operate in a wider range can be driven by business factors.

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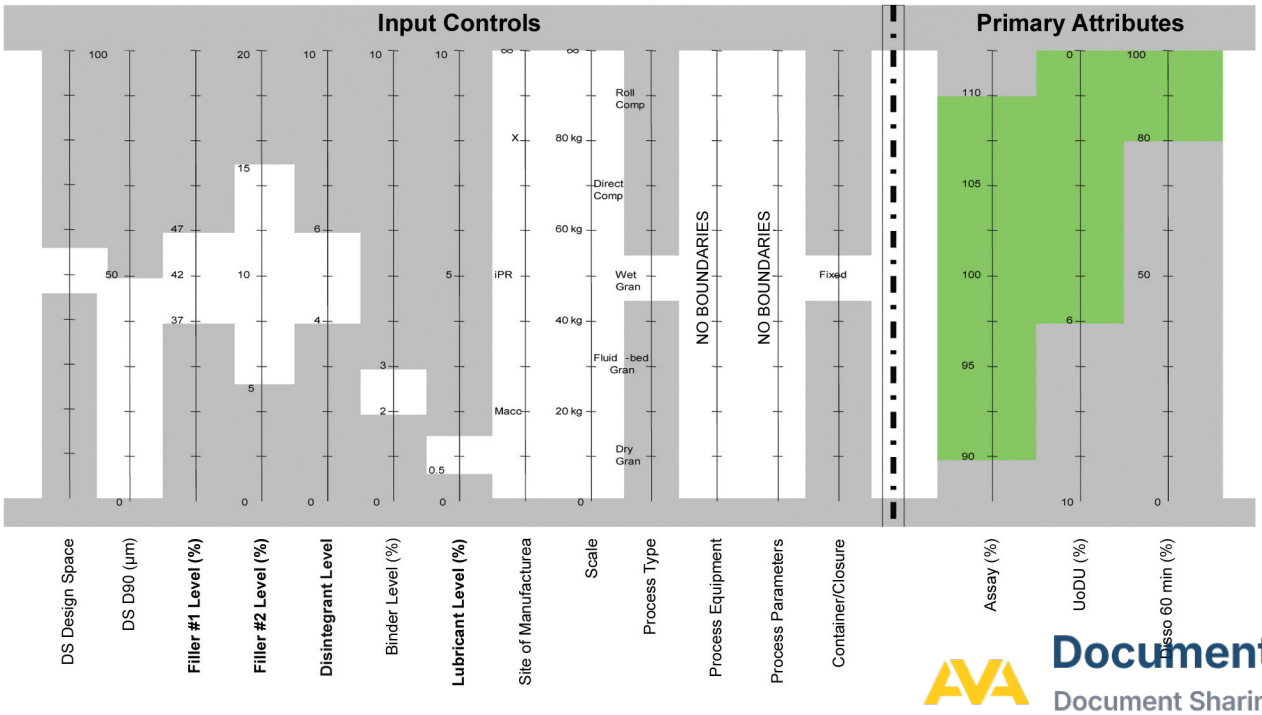
Figure 3.9: Example of Alternate Linearized Design Space Constructs based on Data from Figure 3.7



A weakness of presenting graphs on paper is that they are two-dimensional, allowing clear presentation of a maximum of three-dimensions or variables and if there are greater than three dimensions, use of images on paper becomes difficult.

A way of representing design space where there are multiple input and output variables is as parallel coordinates, an example being given in the Sakura tablet Mock QOS, Figure 2.3.P.2.3-8 developed by a Japan industry team led by Y. Hiyama of the Japan National Institute of Health Sciences (Reference 3, Appendix 1). A similar parallel coordinates' representation is given in Figure 3.10.

Figure 3.10: The Drug Product Design Space



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Parallel coordinates representation has the advantage of being able to present ranges of many critical process parameters and material attributes (input variables) and assurance of quality in the form of multiple CQAs. In Figure 3.10, the critical process parameters and Material Attributes (MAs) for which there are boundaries are presented on the x axis to the left of the vertical bold line. The light shaded areas are the acceptable ranges for each CPP or MA, units being appropriate for each variable. To the right of the bold line are the CQAs required to be achieved with their acceptance criteria shown as lighter gray shading. An acceptable batch has to meet all CPP, MA, and CQA acceptance criteria. A weakness of parallel coordinates is that it is not good at representing complex interactions between input variables. In part, this deficiency can be helped by additionally having an algorithm (or algorithms) also described as part of the design space linking multiple input variables to an output CQA – see Part 2: Illustrative Example.

Another example of a way of representing a design space is as a table, e.g., in the ACE tablets case study developed as part of an FDA Cooperative Research and Development Agreement (CRADA) by the CMC-IM Working Group team (Reference 4, Appendix 1) and this is reproduced as Table 3.5. The two right hand columns of Table 3.5 illustrate that formulation component adjustment may be made to account for the particle size distribution of the ingoing API. The design space elements for the blending and roller compaction steps are based largely on ensuring that the output material attributes are within pre-defined ranges of blend uniformity and relative ribbon density.

Table 3.5: Summary of Overall Design Space for ACE Tablets

Formulation, Blending, Compaction, and Milling Parameters		
Attribute	**Design Space when Acetriptan Particle Size is 10 to 35 microns**	**Design Space when Acetriptan Particle Size is 35 to 40 microns**
Acetriptan Particle Size	d90 10 to 35 microns	d90 35 to 40 microns
Acetriptan concentration	10%	10%
Microcrystalline Cellulose (MCC)	40% (intragranular)	40% (intragranular)
MCC Particle Size (d50)	30 to 90 microns	30 to 90 microns
Croscarmellose Level	3 to 4%	3 to 4%
Lactose Monohydrate	38.75 to 40.75%*	39.00 to 40.75%*
Lactose Particle Size (d50)	70 to 100 microns	70 to 100 microns
Talc	5%	5%
MgSt Level	1 to 2% (intragranular) 0.25% (extragranular)	1 to 1.75% (intragranular) 0.25% (extragranular)
Blender	Any diffusive blender	Any diffusive blender
Humidity	20 to 70% RH	20 to 70% RH
Relative Ribbon Density	0.68 to 0.81	0.68 to 0.81
Granule GSA (cm2/100 g)	12,000 to 41,000	12,000 to 41,000
Hardness (kN)	5 to 12	5 to 12
Mean Core Weight 20 cores	194 to 206 mg	194 to 206 mg
Individual Core Weights	190 to 210 mg	190 to 210 mg
Scale	Any	Any
Site	Any certified site using equipment of same principles	Any certified site using equipment of same principles
*Quantity adjusted to compensate for amount of croscarmellose sodium and/or magnesium stearate (MgSt) used in order to ensure 200 mg overall tablet weight.		

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Further discussion and examples are given in Topic III Design Space and in Part 2: Illustrative Example.

3.7 Control Strategy

Control strategy is defined in Q10 (Reference 7, Appendix 1) as:

"A planned set of controls, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control."

The goal of the control strategy is to ensure that CQA acceptance criteria are always achieved. Using the enhanced, science- and risk-based approach to product and process development, high levels of understanding should be produced, a major goal of the studies being to derive a control strategy or control strategies for implementation in manufacturing and discussion in a regulatory submission.

A company could make a control strategy choice using quality risk management based on several factors:

- patient requirements, minimizing risk to the patient
- regulatory expectations
- company strategy
- effectiveness of pharmaceutical quality system, e.g., the process performance and product quality monitoring system
- cost

A consequence of using the science- and risk-based approach is that there will be increased opportunities to move from manual control of processes to the use of semi-automatic and completely automatic processes using either or both of feed forward or feedback control. As well as ensuring the CQA acceptance criteria are achieved, application of these tools should make pharmaceutical manufacture more efficient. There could be opportunities also to move toward increased real time release testing.

Although proposing a design space is optional, the design space examples given in Q8(R2) (Reference 1, Appendix 1) could be used to consider different control strategy options, and using a design space offers advantages. One advantage is the assurance that operation within the design space will ensure that quality is achieved in terms of meeting CQAs and another is that a flexible and adjustable manufacturing process can be established, i.e., a process where the process parameters described by the design space can be adjusted. In Example 1c in Q8(R2) (Reference 1, Appendix 1), a design space is proposed and this is repeated in Figure 3.7. Using the design space illustrated in Figure 3.7, several control strategies could be considered for introduction to manufacturing:

- set parameter 1 at e.g., a value of 48 and parameter 2 at a value of 0.6
- set parameter 1 at e.g., a value of 46 and allow adjustment of parameter 2 within the range 0 to 1.5
- Monitor parameter 1 perhaps using an on-line technique and adjust parameter 2 in a feed forward process ensuring that both parameters 1 and 2 remain in acceptable regions to achieve the CQA acceptance criteria. This can be a manual control or automated and integrated in the engineering plant control system.

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- Measure the CQA of dissolution on-line, if possible using a PAT tool (often through a surrogate or indirect measure) and feedback to adjust parameters 1 and 2 manually or via automatic control system to ensure CQA meets acceptance criteria.

Choice of which option to use could depend on the factors listed above.

Understanding and control of parameters 1 and 2 and their relationship to dissolution are the most important features of this control strategy and should be discussed in a regulatory submission. Other lower risk elements of the control strategy could be dispensing of materials into the granulation which, since variability of dispensing does not affect dissolution, is a non-critical process parameter and is controlled by the quality system. Therefore, the unit operation of dispensing is probably not discussed in detail in a regulatory submission. However, these lower risk elements are still a component of the control strategy. Parts of the control strategy covered by good manufacturing practice regulations have their own risk profile depending on the product and process and in some cases may not be low risk. For example, for an aseptically-produced product using a non standard process, factors such as design and operation of facilities as well as operator training could be the highest risk elements in a control strategy.

Implementing this control strategy in manufacturing should be risk-based and may require an update of the Pharmaceutical Quality System (PQS) to address issues such as:

- How are parameters 1 and 2 controlled and who has responsibility?
- What backup procedures are there if anything goes wrong?
- How are operators trained?

Any impact on the quality system, including definition of responsibilities and provisions for managing potential failures of the PQS should be understood and the PQS updated, as required.

Development of a control strategy provides the tools for measurement of parameters and attributes identified in the control strategy, and should provide the basis for analysis of these data. Evaluation of data emerging from the application of the control strategy should provide the primary internal source of feedback on product quality for input to the Process Performance and Product Quality Monitoring System.

The batch release strategy will be based on the control strategy for a particular product, and should take account of regulatory expectations and the company quality system (Reference 15, Appendix 1).

Further discussion and explanation of control strategy and its implementation into manufacturing is given in Topic IV Control Strategy and Part 2: Illustrative Example.

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4 Continual Improvement

ICH Q10 Section 3 (Reference 7, Appendix 1) describes Continual Improvement, which is applicable to all products, not only those developed using the enhanced approach. Certain GMP requirements also apply however a product was developed.

The sub-section on Lifecycle Stage Goals in Q10 (Reference 7, Appendix 1) describes the goal of pharmaceutical development and refers to pharmaceutical development (Q8(R2)) (Reference 1, Appendix 1) which is further elaborated in this Overview, and the goals of technology transfer, commercial manufacturing, and product discontinuation. When developing a product using a science- and risk-based approach, it is anticipated that experimental studies consider the impact of change of scale and equipment and ways of working involve both development and manufacturing personnel such that the technology transfer step mentioned in Q10 (Reference 7, Appendix 1) evolves from repeatability-type studies to continued process verification – see Section 3.5.3 for more information on Scale of Studies.

Part of Technology Transfer is process validation and FDA has issued revised guidance (Reference 16, Appendix 1), which has three stages of process validation – process design, process qualification, and continued process verification. Developing and transferring products to routine production in line with a more structured science- and risk-based approach should meet the technical expectations of this FDA guidance. For example, DoE studies during development increasingly should be the norm, as discussed earlier in the Overview and mentioned in the FDA guidance, giving more information to derive a control strategy and establish science-based process qualification protocols, and continued process verification programs. EMA is revising its Guideline on Process Validation (Reference 17, Appendix 1) to take into account the latest ICH concepts and FDA developments. ASTM has produced some standards which may be useful to practitioners qualifying equipment and facilities and applying continued process verification (References 18 and 19, Appendix 1).

Continued process verification is an on-going program to collect and analyze product and process data that relate to product quality including relevant process trends, quality of incoming materials or components, in-process materials, and finished products. The goal of continued process verification is to continuously monitor and evaluate a process to assure it remains in a state of control (validated) throughout the commercial part of the product lifecycle. Therefore, continued process verification is part of an effective process performance and product quality monitoring and CAPA systems.

Innovation as well as outputs of process performance and product quality monitoring, CAPA, and management review of process performance and product quality systems provide assurance of a state of control as well as drive continual improvement, which is implemented using the change management system. These systems provide feedback on product quality from both internal and external sources, e.g., in-process controls, finished product specifications, analysis of parameters, and attributes identified in the control strategy to verify continued operation within a state of control, complaints, product rejections, non-conformances, recalls, deviations, audits, and regulatory inspections and findings.

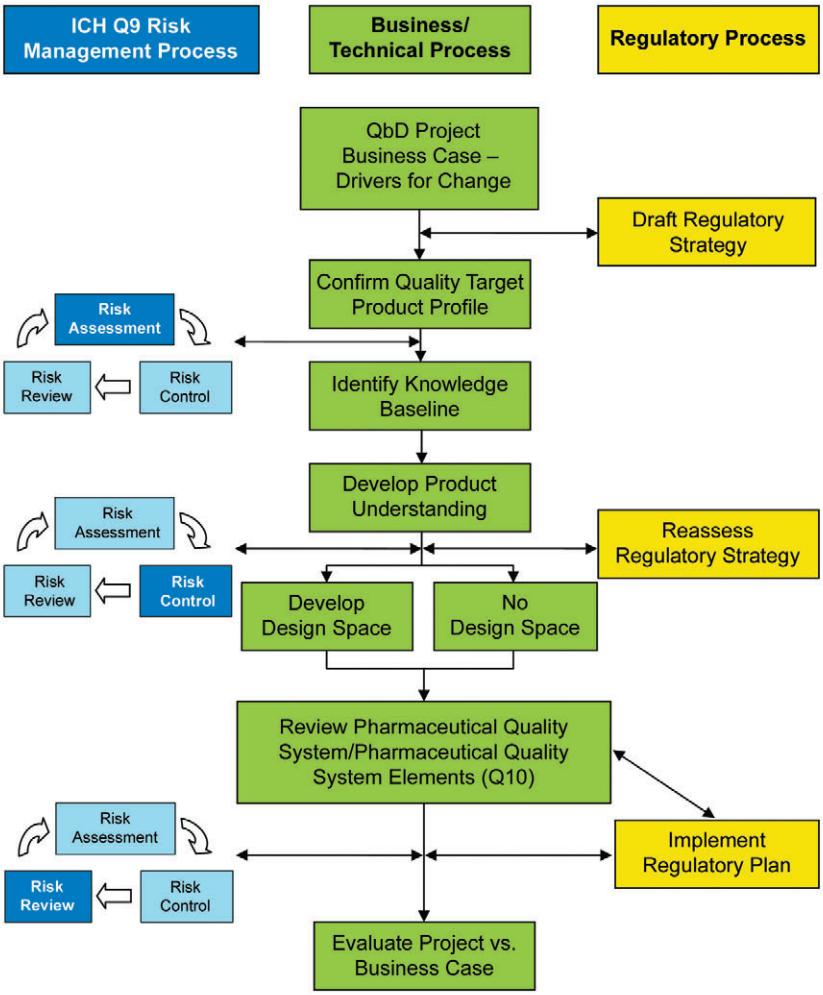
For example, root causes of defects and/or unacceptable variability of quality attributes can be identified using a variety of statistical tools, e.g., process behavior or process capability measures, and potentially reduced or mitigated through disciplined and data driven Six Sigma or equivalent methods to propose opportunities for continual improvement.

Reducing variability or tightening acceptance criteria with no additional benefit to the patient is of no value, and an unnecessary cost. Products developed and manufactured using QbD should give much better estimates of variability to include in the process performance and product quality monitoring system leading to better estimates of how much optimization is required. However, there are opportunities other than reducing variability for continual improvement such as reducing waste, improving equipment, and facility utilization. Proposed changes should be evaluated and tracked by a company's change management system.

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There may be opportunities and benefits from continuing to apply QbD principles to a product developed using QbD as discussed in this document. There also could be opportunities to use QbD principles to an existing product developed using the science applicable at that time, which may not have involved a QbD approach. Figure 4.1 (Reference 10, Appendix 1) contains a process flow that summarizes business, technical, and regulatory considerations when implementing science- and risk-based approaches for existing products. A project emerging from the process described in Figure 4.1 would be considered continual improvement and would follow the Lifecycle Management arrow in Figure 3.1 where a project would cycle back from continual improvement to review of current knowledge.

Figure 4.1: Process for Applying Science- and Risk-Based Approach to an Existing Product



Three case studies are included (Reference 10, Appendix 1). In one case study, flexibility of addition of water amount for a granulation was justified using a unit operation design space. In another case study, a manufacturing step was removed justified using quality risk management without using a design space, and in the third case, real time release testing was justified for a solid oral dosage form, again without proposing a design space based on extensive process knowledge and additional process understanding studies. All products that formed the basis of these case studies have been approved by least one regional regulatory agency.

It is anticipated that a science- and risk-based approach to continual improvement could be applied to an existing product at any stage in the lifecycle post approval, and to any type of existing product, including a generic or self-medication/Over-the-Counter (OTC) product.

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5 Benefits of Using QbD in Development

The following benefits of a science- and risk-based approach to support product realization are discussed below.

- making development more efficient
- improving manufacturing efficiency
- proposing regulatory flexibility
- business strategy
- environment

The business case to justify ICH Q 10 (Reference 7, Appendix 1) topic has good examples to justify the science- and risk-based approach (Reference 20, Appendix 1). A further example of a summary of the financial benefits of using this approach is given in the Gold Sheet (Reference 21, Appendix 1), which in turn refers to a McKinsey report.

5.1 Making Development More Efficient

The use of a science- and risk-based approach has the potential over the lifecycle of a product to use less resource, materials, and time compared with a conventional approach for a given level of output. Although such an approach may require more resources, time, and effort initially, it is not seen as extending time to market, but rather a **new way of working** being more scientific and systematic. The benefits are reduced time and resources to scale-up, transfer, commercialize and maintain products, and more efficient and robust manufacture.

Potentially timelines for development studies may be easier to estimate, particularly later in programs. Data are hard to estimate and should emerge in the next few years since a science- and risk-based approach does require upfront investment and the payback comes later in the lifecycle. Calculations are made more difficult by the need to estimate effort invested in products which do not reach the market, and by different companies taking different approaches regarding the amount of effort to expend on a project which itself has high risk, e.g., clinically.

A key feature of the science- and risk-based approach as discussed in Section 3.5, Product and Process Development, is that there is need for more multi-disciplinary working than has been the case. In the past, R&D often has worked independently of Manufacturing during development, and vice-versa, Manufacturing has made **improvements** to existing commercial processes without consulting R&D. This increased multi-disciplinary working is highly desirable to optimize output from risk assessment exercises, even during early development, and also when designing experimental studies. Again hard data to support that this cooperative working structure improves efficiency are still to be developed and published; however, there are many subjective reports that this cooperative working is a benefit. It is not possible to recommend ideal working processes or structures since companies have many different organizational and budgetary structures, and they will seek to introduce this approach in a way appropriate for them.

Companies will decide when in the development program from pre-clinical studies to Phase 3 it is appropriate to consider starting enhanced development work and there will be variation depending on company strategy and project. For example, with biotechnological compounds, there is a stronger case to start the work early, even for preparation of pre-clinical batches, and there could be significant prior knowledge from the use of **platform technologies** that have been applied to previous projects.

For small molecule projects, the science- and risk-based approach work could be started early, especially with drug substance process development; however, it also could be delayed until after a proof of concept clinical decision when investment of significant resource should be easier to justify. Many companies have the strategy to use the commercial formulation in Phase 3 clinical studies so there is an opportunity to commence work before Phase 3 and continue in parallel with Phases 3 studies.

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5.2 Improving Manufacturing Efficiency

There are many opportunities for improving manufacturing efficiency (Reference 20, Appendix 1), including:

- reducing variability of a process and increasing predictability of manufacturing output, i.e., making the process robust
- reducing manufacturing cycle-time
- reducing inventory
- optimizing equipment selection and utilization
- minimizing technical problems
- maximizing yield
- optimizing cost of quality
- optimizing amount and complexity of analytical testing
- optimizing post approval stability programs
- introducing real time release testing
- improving assurance of product quality
- developing meaningful, science- and risk-based product validation plans (Stages 2 and 3)

Traditional pharmaceutical manufacturing and associated regulatory submissions have been based on the concept of a fixed process, which can lead to high process variability and hence, high output variability, resulting in processes that are only of the order of 2.5 to 4.5 sigma-capable (Reference 20, Appendix 1). In contrast, manufacturing processes developed with a science- and risk-based approach establish a manufacturing environment where the relationships between material attributes, process variables, and quality attributes are well understood.

Based on this process understanding, the process may be adjusted to respond to input variability and variability of process parameters ultimately to provide for reduced variability of output resulting in processes approaching or achieving Six Sigma capability. Movement toward these reduced levels of variability leads to significantly improved and predictable output from manufacturing with reductions in inventory levels and the cost of supply. If this is achieved, product can be manufactured **just in time** as in other industries rather than manufacturing for inventory levels estimated based on predicted requirements.

Additionally, there are many other associated benefits such as shorter cycle times and increased yields, fewer investigations, more information on which to base root cause analysis, and an overall reduction in the costs of internal failures (i.e., rejects, reworks, reprocessing, extra set ups, process downtimes, emergency purchases of materials, and investigations). More efficient manufacturing should optimize use of management time, use of equipment, and size and use of facilities, and some companies have reported that using the science- and risk-based approach these benefits are significant (Reference 10, Appendix 1).

Other potential benefits from increased product understanding are in reduction and simplification of analytical testing and potential reduction in post approval stability programs.

Increased understanding could lead to real time process control of some unit operations and to real time release testing for all or some attributes in a specification.

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Processes and their controls also may be fully or partly automated minimizing the variability from human interaction.

Development of products using the enhanced, QbD approach should assist in meeting the expectations of Stage 1 of FDA Process Validation Guidance, and be a baseline for progressing to Stages 2 and 3.

5.3 Proposing Regulatory Flexibility

Opportunities should be available when proposing a design space since "working within the design space is not considered as a change" (Q8(R2) (Reference 1, Appendix 1)). It should be possible using the higher levels of understanding to facilitate manufacturing process improvements, within the approved design space described in the dossier, without further regulatory review and leading to a reduction in post approval submissions. However, in the enhanced approach, establishing a design space is not necessarily expected.

It is likely for companies with little prior experience that compilation of a regulatory submission using the enhanced approach will be more challenging and time-consuming than the traditional submission and certainly may require more interactions with regulators during the development and pre-submission phases to reduce uncertainty for a company and give the regulators opportunity to input to the program and prepare for review and investigation.

However, an objective is that the investment in technical work and regulatory dossier compilation and submission will lead to the opportunity to make improvements using the company pharmaceutical quality system. One of the drivers for a company to make improvement using its PQS is to have more control of timing of introduction of these improvements.

Some examples of **regulatory flexibility** achieved by companies are given in the paper applying the science- and risk-based approach to existing products (Reference 10, Appendix 1), including:

- introduction of a flexible process
- reduction in stability programs
- reduction in number of process steps
- introduction of real time release testing

These examples were justified by the companies based on their specific case and enhanced understanding, and opportunities and justification will vary from case to case.

Other possibilities are given in the regulatory Section of the A-Mab case study (Reference 5, Appendix 1). This Section is provided to stimulate discussion about how the knowledge and data exemplified in this case study can be used to create risk-based regulatory strategies for product licensure and management of changes to the manufacturing process.

5.4 Business Strategy

As an alternative or addition to a potential business strategy of improving manufacturing efficiency for a product, there is other flexibility that a company may wish to achieve, such as introducing the ability more easily to move processes between sites, to change scales to meet demand, and/or to operate processes using a variety of equipment.

Some companies have considered that projects developed using QbD allow technical and manufacturing employees to understand better the needs of their **customers**, and to introduce cultural change with more multidisciplinary teams, e.g., involving R&D working alongside manufacturing and encourage better interactions between scientists and their management.

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Additionally, such projects have been used by companies to understand better regulatory agency implementation of new guidelines and to improve a company's interactions with regulators.

5.5 Environment

The cost pressures on the pharmaceutical industry and the regulatory agencies mean that they need to do what is necessary to ensure that products are manufactured and regulated as efficiently as possible. The result has been that both industry and regulators express a real desire for changes. From industry, there is a need to reduce costs by ensuring processes are developed efficiently and products manufactured as efficiently and robustly as possible. Data are beginning to emerge from companies regarding experiences with filings, which include QbD elements (see case studies in Reference 10, Appendix 1).

There is also a change in the technological environment, which supports use of QbD. There is increased availability of more sophisticated and easier to use software packages for use in Design of Experiment (DoE) studies and the development and understanding of multi-factorial models of processes provides the ability realistically to push forward science- and risk-based approaches. The new technical environment may help to overcome resistance that has been encountered with some scientists when asked to consider multi-factorial over univariate approaches in product development and process improvement for existing products.

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Topic II
Criticality

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6 Introduction

6.1 Overview

The purpose of this topic is to identify and characterize how industry determines critical quality attributes for a drug product and critical process parameters in the manufacture of drug product and drug substance, and subsequently develop simple guidance for applying these approaches consistent with ICH Q8(R2), Q9, and Q10 (References 1, 7, and 8, Appendix 1).

This topic gives tools, explanatory guidance, and examples relating to assignment of criticality for both critical quality attributes and critical process parameters (and critical material attributes).

For drug product quality attributes, it is proposed that the "level of criticality" is determined primarily by severity of impact. A factor for "uncertainty" also may be considered to accommodate the lack of certainty (i.e., uncertainty) of translation/extrapolation of a proposed quality attribute to the level of severity of harm to patient safety and efficacy.

For process parameters and material attributes, ICH guideline designation of criticality is a function of variability. This topic elaborates and expands criteria for assessing and characterizing risk relative to probability, thereby proposing a continuum of risk and, by extension, a continuum of criticality. Finally, the level of risk may be reduced by estimating and/or demonstrating how detectable the risk is. For this reason, the establishment of an appropriate and robust control strategy is fundamentally predicated on understanding critical quality attributes and critical process parameters and critical material attributes.

6.2 Objective

This topic suggests approaches and gives guidance and examples toward assigning criticality to drug product and drug substance quality attributes, and to process parameters and material attributes using application of quality risk management.

6.3 Scope

This topic provides guidance to enable the separation of what is critical, through the "continuum of criticality" from what is less critical or non-critical. It is not intended to describe how to perform risk assessments. The approaches for identifying, assessing, evaluating, and communicating risks are well described in the literature as well as in ICH Q9 and in other parts of this Guide Series, for example, Topic III Design Space.

This topic provides context for the delineation of criticality during product development and throughout a product's commercial lifecycle (i.e., during product realization). The subject of this topic is intended to be complementary to ICH guidelines. However, the content is not intended to be prescriptive. It is also not a regulatory guideline, but rather a technical perspective that offers options for how criticality may be assigned.

6.4 Benefits

Given that ICH guidelines do not define "critical" and the word is used frequently in these guidelines, some guidance in how to assign "criticality" is warranted. Discussion and examples in this topic in combination with examples of risk assessment procedures in Topic III Design Space and examples of criticality assignment in Part 2: Illustrative Example provide guidance and tools to help propose criticality assignments in attempt to assist companies present their case for these assignments.

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6.5 Key Concepts

This section uses as a basis concepts, guidance and definitions given in ICH guidelines, Q8(R2), Q9, Q10, and Q11, Step 2 (References 1, 6, 7, and 8, Appendix 1) as well as subsequently issued Points to Consider document (Reference 15, Appendix 1). Definitions of relevance to this topic are:

Critical Quality Attribute (CQA):

A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. (ICH Q8(R2))

ICH Q8(R2) says "CQAs are generally associated with drug substance, excipients, intermediates (in-process materials) and drug product."

Critical Process Parameter (CPP):

A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality. (ICH Q8(R2))

A definition of critical material attribute is not given in the above ICH guidelines; however, the assumption in this document is that the definition would be based on that for a CPP.

Risk:

The combination of the probability of occurrence of harm and the severity of that harm. (ISO/IEC Guide 51, ICH Q9)

Although the phrase, "level of criticality," is not used and "critical" is not defined in any of the ICH guidelines, there is general agreement within the industry that assigning criticality to an attribute, parameter, or variable can be relatively subjective and dependent on context. While a critical attribute or parameter is frequently interpreted as connoting "high risk," judgments of how high is "high" and what does "high" mean from a regulatory perspective remain debatable and inconsistent from company to company as well as among regulatory authorities. Consequently, criticality is considered related to risk, and therefore, this topic discusses the application of quality risk management (Q9) to the assignment of criticality.

6.6 Structure of This Topic

This topic discusses:

- background
- review of industry experience
- the context of criticality
- the importance of criticality
- use of risk management in assignment of criticality
- approaches to assigning CQAs and CPPs
- use of criticality throughout the product lifecycle

Documents
Document Sharing Hub

Full document details: ISPE Guide Series PQLI Part 1 - Product Realization using Quality by Design (QbD) - Concepts and Principles 2011